Management of Cancer Associated Thrombosis (CAT) – where data is lacking

Tim Nokes

Haematologist, Derriford Hospital, Plymouth

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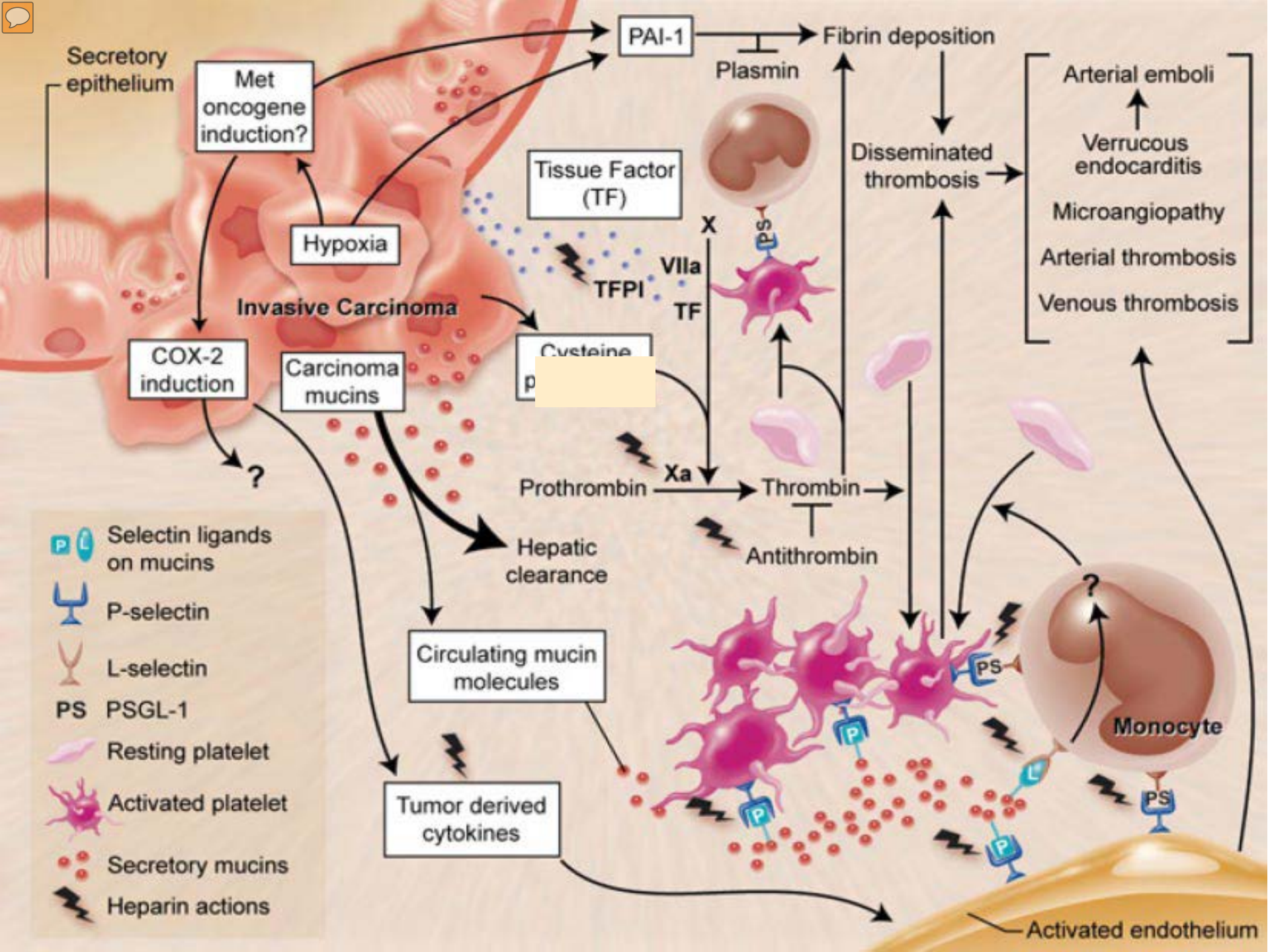
Cancer-associated VTE *(Thein et al 2016)*

- Cancer-associated thrombosis (CAT) accounts for about 20% of all thrombosis worldwide.
- Risk for VTE in cancer patients is 4-7 times higher than baseline.
- Risk for recurrent VTE, 3 times higher in cancer patients compared to those without Cancer.
- Survival of cancer patients with VTE, lower than that of patients without VTE - ?effects of VTE or increased tumour aggression

Why does Cancer increase the risk for VTE? *(Watson H, BCSH 2015)*

- Expression of tissue factor and cytokines on tumour cells & microparticles
- Interaction between tumour cells and endothelium, causing endothelial damage & platelet activation
- Prothrombotic properties of Mucins
- Mass effect impairing venous return
- Surgery, IV catheters, chemoradiotherapy & intercurrent medical problems eg infection


Secretory epithelium
Met oncogene induction?
PAI-1
Fibrin deposition
Plasmin
Arterial emboli
Verrucous endocarditis
Microangiopathy
Arterial thrombosis
Venous thrombosis
Disseminated thrombosis
Tissue Factor (TF)
Hypoxia
X
PS
VIIa
TFPI
TF
Invasive Carcinoma
COX-2 induction
Carcinoma mucins
Cysteine
?
Prothrombin
Xa
Thrombin
Antithrombin
Hepatic clearance
Circulating mucin molecules
Tumor derived cytokines
Monocyte
Activated endothelium
Selectin ligands on mucins
P-selectin
L-selectin
PS PSGL-1
Resting platelet
Activated platelet
Secretory mucins
Heparin actions

Chemotherapy

In dwelling catheter

Hospitalisation

CANCER

Surgery

Radiotherapy

Sepsis

Imaging

VTE & Cancer

- VTE is second most common cause for death after the malignancy itself in cancer patients *(Korhana 2010)*
- Highest risk sites are: Lung, brain, pancreas, stomach, ovary, kidney, Lymphoma & Myeloma
- VTE + Cancer also leads to increased risk for hospitalisation, bleeding, recurrent VTE on anticoagulants *(Trujilo-Santos 2008)*

Investigating patients with unprovoked VTE for Cancer - background

- Historically, 'unprovoked' VTE associated with occult cancer in 10% of patients within a year *(Carrier, 2008)*
- NICE: CG 144 (2012) states that in patients >40 years, with first unprovoked VTE, CT scan of abdomen & pelvis (& mammograms in women) is recommended.
- More recent data has placed the incidence of occult cancer lower at 4%

CT scans for unprovoked VTE

- CT scans convey a high exposure to radiation – equivalent to 234 CXRs or 39 mammograms
- Psychological and biological morbidity may be associated with further investigations
- Significant cost associated with false positive findings ('incidentalomas') requiring further investigations
- Incorrect to assume that earlier detection results in improved clinical outcomes

Suggested routine screening for unprovoked VTE

- History: Older age, smoking
- Worrying symptoms:
  - Weight loss
  - GI bleeding
  - Constitutional symptoms
- Physical examination
- CXR
- Basic blood tests:
  - FBC, Ca, LFTs, PSA, Igs,
- Urinalysis

Cancer screening in VTE (SOMIT study)
2 years follow-up

Screened group

- 13/99 detected occult cancer by 1/12
- 1 cancer became apparent later
- Cancer related mortality 2.0%

Non-screened group

- 10/102 developed cancer later – mean of 11.6 months
- Cancer related mortality 3.9%

Piccioli et al JTH 2004

VTE cancer screening: 630 idiopathic VTE

	Extensive Screen	Standard Care	HR 95% CI
All cancers	8.8%	7.3%	
Curable Ca	3.8%	3.8%	
All cause mortality	7.6%	8.3%	1.22 (0.7-2.2)
Cancer death	5%	2.8%	1.8 (0.75-4.3)

Associated cost analysis: Routine screening = E165 v Extensive screening = E530 mainly investigating from false positive findings (86 patients)

Van Doormaal et al JTH 2011

Guidance for the prevention and treatment of cancer-associated venous **thromboembolism**. *(Korhana A. 2016)*

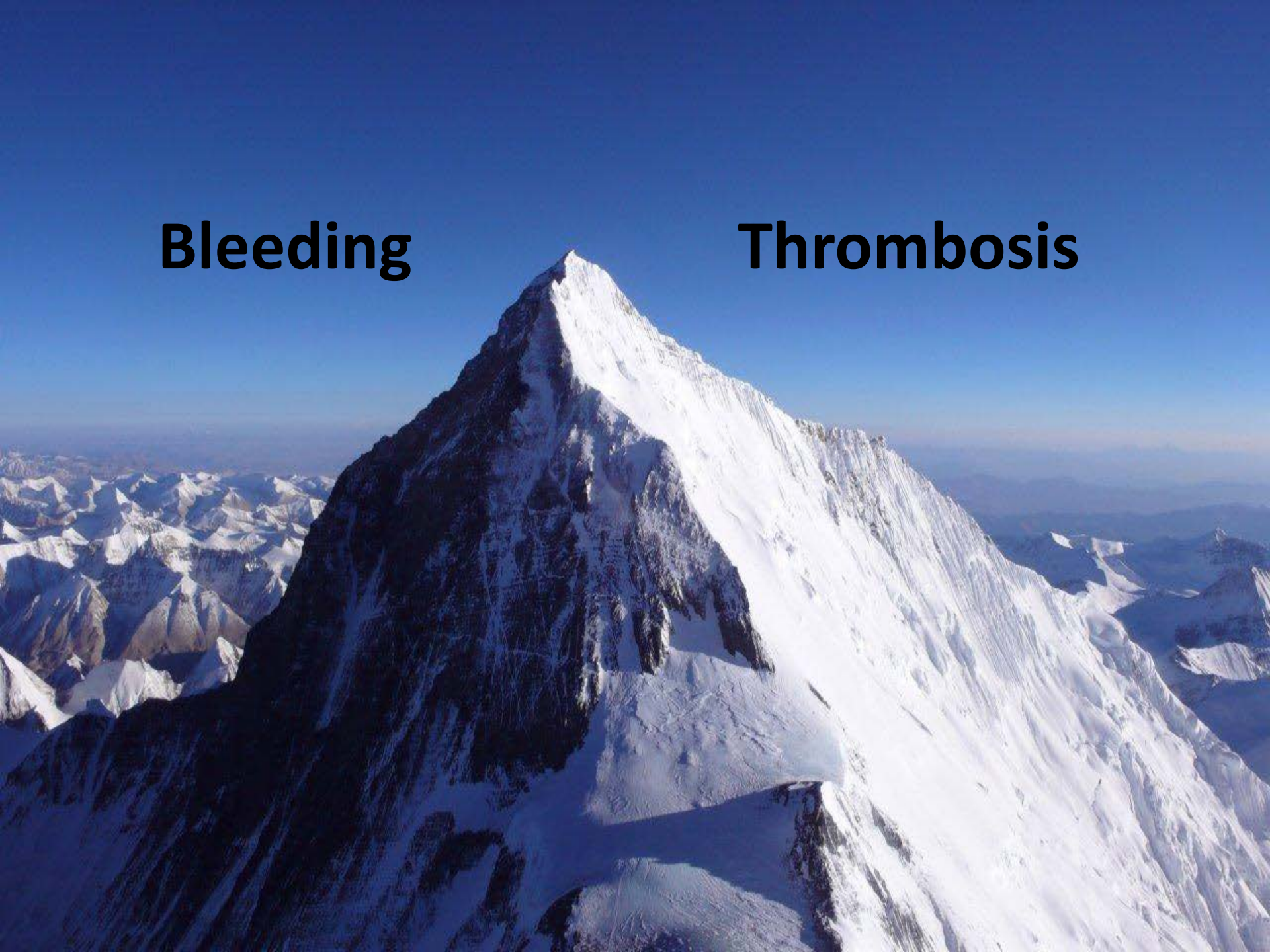
- *Patients with unprovoked VTE should undergo a through medical history and physical examination, basic laboratory investigations (complete blood counts, metabolic profile and liver function tests) and chest X-ray.*
- *We suggest that if not up-to-date, patients undergo age and gender-specific cancer screening (i.e. cervical, breast, prostate and colon)*

Limited v Extensive Cancer screening in unprovoked VTE *(Khan F, BMJ 2017)*

Study	Study & (Size)	Frequency of occult Cancers diagnosed	Cancer deaths	Quality of evidence
Robertson 2015	Cochrane review of 2 studies (396)	OR 1.32 (P=0.5)	OR 0.49 (P=0.26)	Moderate
Carrier 2015	RCT (845)	19 v 14 (P=0.28)	1.4% v 0.9% (P=0.75)	High
Robin 2016	RCT (394)	4 v 11 (P=0.065)	2.5% v 1.0%	High
Prandoni 2016	RCT (195)	8 v 10 (P=0.81)	4% v 2%	Moderate
Salih 2016	Meta-analysis unpublished (1250)	OR 1.36 (P= 0.25)	OR 0.57 (P=0.22)	Unknown

What should we tell patients currently?

- NICE states: ‘Consider’ screening for cancer with CT
- Most recent data suggests 1 in 25 people with unprovoked VTE may have underlying cancer
- Limited evidence to support the benefit of extensive screening, particularly involving harm from ionising radiation.
- All such patients should receive routine cancer screening plus additional investigations depending on signs and symptoms
- If patients opt out of CT scanning, maintain low threshold for suspicion of cancer


Bleeding
Thrombosis

Thrombocytopenia *(BCSH, 2015)*

- When present, the risk-benefit balance of anticoagulation needs reassessment
- In first 3 months after VTE, risk for recurrence is higher - every effort should be made to maintain safe administration of therapeutic anticoagulation.
- Full anticoagulation is probably safe when platelets are >$50x10^9$/l *(Carrier 2013)*

Thrombocytopenia in CAT: Considerations

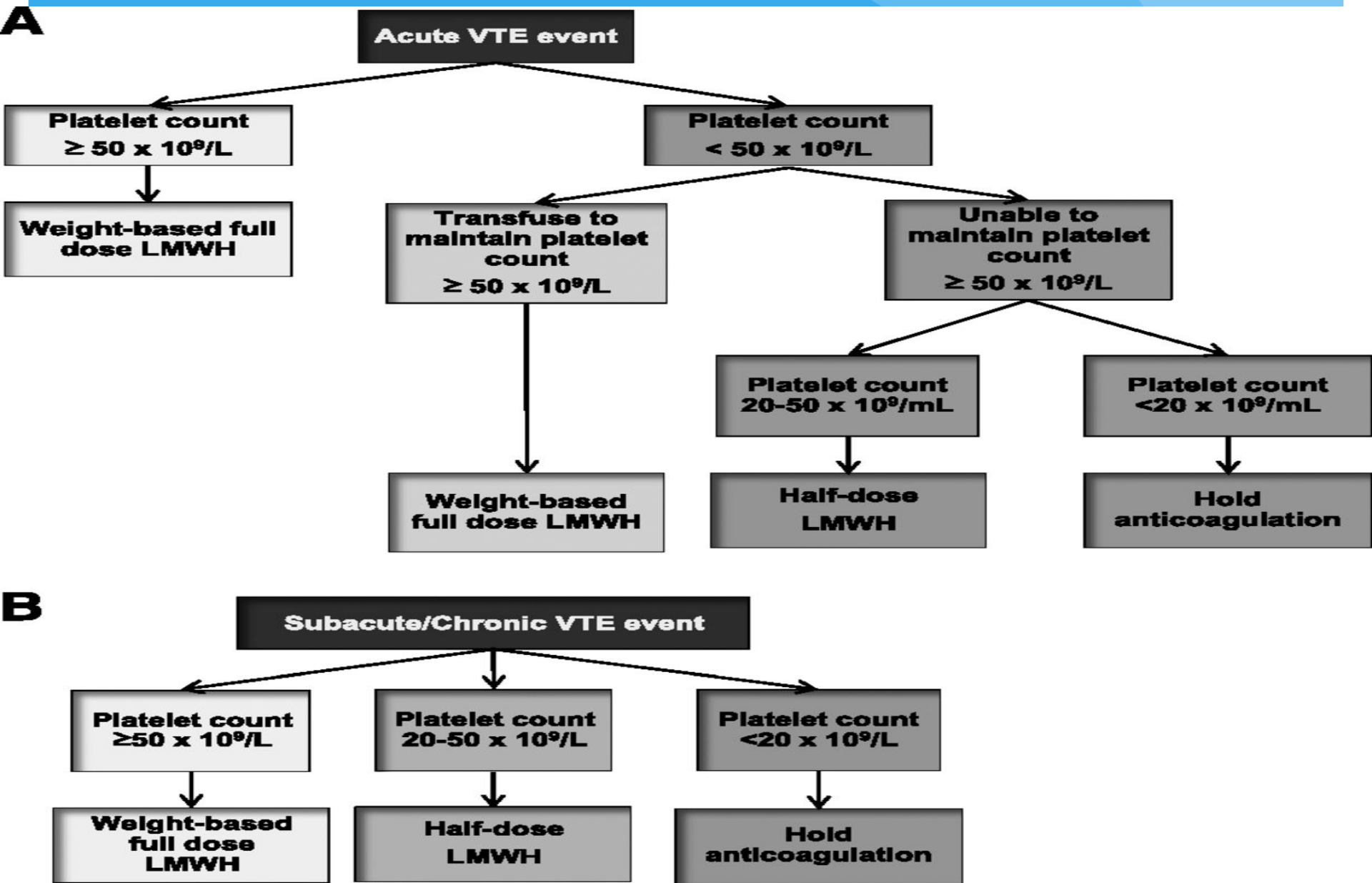
- Causes (consider potential to reverse):
  - Chemotherapy effect
  - ITP
  - DIC
  - TTP
  - HITT
- Increased risks for bleeding
  - Advanced age,
  - Renal failure
  - Abnormal clotting eg Vit K deficiency

Thrombocytopenia, Cancer & VTE *BCSH, 2015*

- Support platelet count (to >50 $x10^9/l$) to allow full dose anticoagulation to continue through highest risk period for recurrence (3/12). (2D)
- Temporary IVC filter should be considered if thrombocytopenia is persistent and difficult to overcome or other bleeding risk is present.
- If platelet count cannot be increased, then consider giving 50% dose LMWH with platelets 25-50 $x10^9/l$ with frequent assessment (2D)
- Below 25 x $10^9/l$, withhold anticoagulation (1D)
- Some evidence that prophylactic LMWH dose may be beneficial (Drakos, 1992)

Thrombocytopenia in patients with CAT

(Lee A, Blood 2013 122:2310-2317)



Risk of Bleeding associated with Anticoagulation in patients with CAT

- Increased risk for bleeding in patients with CAT receiving VKA – 12%. 1/3 in initial stage of anticoagulation *(Prandoni, 2002)*
- No correlation between risk for bleeding and INR level in patients with cancer *(Paleretti 2000)*
- Similar bleeding rates: LMWH & VKA *(Hull 2006)*
- Bleeding risk in cancer patients dependent on many patient factors: Type and location of Ca, need for biopsies, thrombocytopenia, DIC, renal & liver impairment and sepsis.

Management of Bleeding associated with anticoagulation in patients with CAT *(BCSH)*

- Individual assessment of bleeding versus recurrent thrombotic risk before starting anticoagulation.
- Minor bleeding: continue full dose anticoagulation with close follow-up
- In patients with moderate to serious bleeding or absolute contraindications to anticoagulation: withold and consider IVC filter.
- Platelet transfusions may allow anticoagulation according to previous flow-chart

Recurrent VTE in cancer patients

- Cancer confers higher risk for recurrent VTE than those without cancer (4-fold increase)
  - Both during & after anticoagulation
- Assess for compliance with anticoagulation
- Assess for mechanical compression of large vein from tumour masses
- Consider HITT
- Registries show very heterogeneous approach to recurrent VTE in patients with cancer

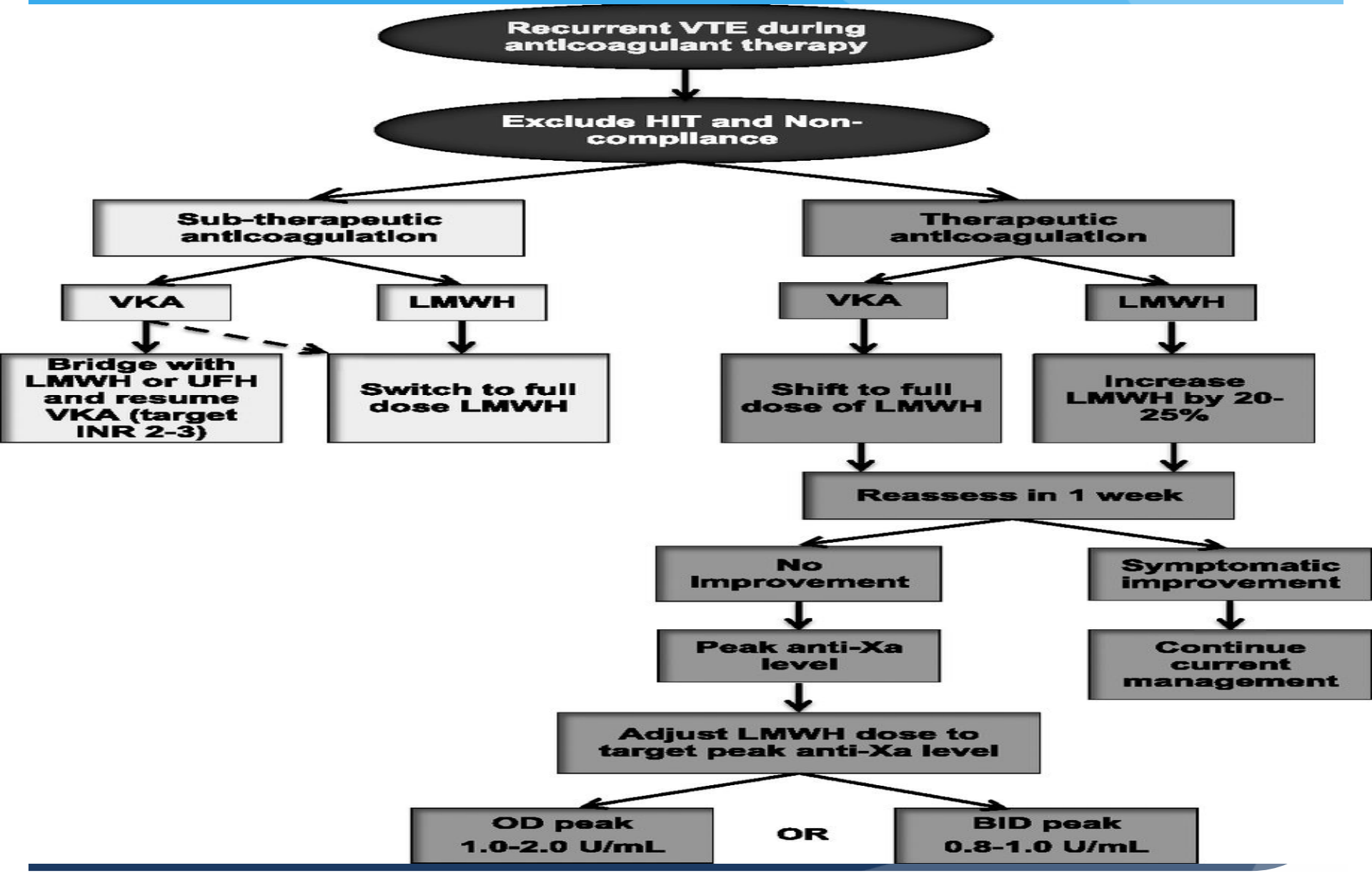
Anticoagulation for Recurrent VTE in CAT

- The optimal duration of primary anticoagulation in CAT is unknown *(NICE suggests 6 months & review)*
- Patients with recurrent VTE can either be:
  - Bridged with LMWH if on VKA
  - Transitioned to treatment dose LMWH if already using prophylaxis
  - Treated with full dose escalation (eg Enoxaparin 1mg/kg twice daily)
- If primary anticoagulation discontinued because of bleeding risk, consider IVC filter. This may not reduce recurrence risk *(Decousus 1998)*

Cancer Patients with Symptomatic Recurrent VTE (*Korhana A. J Thromb Thrombolysis. 2016)*

- Therapeutic anticoagulation with an agent **other** than LMWH: Transition to therapeutic LMWH.
- Optimal anticoagulation with LMWH: Continue LMWH at a higher dose, starting at an increase of ~25 % of the current dose
- Non-therapeutic dose at the time of recurrence: Switch to therapeutic dose of LMWH
- Do not use IVC filters except in presence of absolute contraindications to anticoagulation (e.g. active bleeding). Retrievable filters should be used.

Recurrent VTE in CAT *(Lee A, Blood 2013)*



Summary

- Cancer increases VTE risk 4 fold
- Those with cancer & VTE have worse prognosis
- CT scanning for patients with unprovoked VTE identifies cancer in about 4% of people. Current advice is that routine screening and clinical history generally sufficient to rule out cancer.
- Bleeding is generally higher in anticoagulated Cancer patients
- Thrombocytopenia is relatively common and needs monitoring in those anticoagulated with CAT, with platelet support if necessary
- Bleeding needs careful assessment of patient and IVC filter if anticoagulation essential
- Recurrent VTE requires increased anticoagulation where possible

Preventing Catheter-related thrombosis

- Prospective study *(Bern 1990)*: 82 patients showed benefit of low dose warfarin in reducing risk of catheter-related thrombosis
- WARP study *(Young 2009)*: RCT of 812 patients randomized to warfarin or no therapy found no difference in risk for catheter-related thrombosis.
- Cochrane review *(Akl 2011)*: demonstrated that neither warfarin or prophylactic LMWH reduced risk for catheter-related thrombosis
  - **Routine anticoagulation is not recommended (1A)**

Thromboprophylaxis in cancer patients admitted to hospital

- Patients with active cancer should be considered for thromboprophylaxis when admitted to hospital, as long as benefit outweighs risk for bleeding. (Kahn, 2012)
- ‘Active Cancer’ should be considered in those diagnosed or treated within the previous 6 months or recurrent / metastatic cancer.

Thromboprophylaxis in ambulatory Cancer patients

- Cochrane review of 9 RCTs (3538 patients) in cancer patients, comparing controls against LMWH (8) or warfarin (1), found reduction in VTE risk with LMWH, without a significant increase in bleeds *(DeNisio, 2012)*
- 60 patients treated to prevent 1 VTE, indicates that TP should not be routine but considered in those with particularly high VTE risk *(BCSH, 2015)*
- Identification of these high risk patients may be done using scoring systems *(Khorana 2008, Farge 2013)*

Predictive model for Chemotherapy-related VTE (Khorana et al 2008)

Patient characteristic	Risk score
Very high risk for VTE: stomach & pancreas	2
High risk for VTE: Lung, NHL, Gynae, bladder, testicular	1
Pre-chemotherapy platelet count	1
Haemoglobon level <100g/l or use of ESA's	1
Pre-chemotherapy leucocyte count >11 x 10^9/l	1
Body Mass Index >35 kg/m^2	1

Score	Actual Score	Thrombosis rate per 2-5 months (%)
Low	0	0.3 – 0.8
Intermediate	1-2	1.8 – 2.0
High	>2	6.7 – 7.1

Incidental VTE

- Cancer patients with incidental PE or DVT should be therapeutically anticoagulated as for symptomatic disease (1C)
- In Plymouth about 50 incidental VTE events per year for last 6 years.
- >75% of these are cancer-related events.
- >75% dead one year later.